UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, DC 20460

AUG 29 1996

OFFICE OF PESTICIDE PROGRAMS
Health Effects Division

MEMORANDUM

SUBJECT: Benoxacor: Review of Supplementary Data Package on Benoxacor

TO: Kerry Leifer - Team Leader
Registration Support Branch, Registration Division (7505W)

FROM: David S. Liem, Ph.D. David Liem 8/12/96
Section II, Toxicology Branch II, HED (7509C)

THROUGH: Clark Swentzel, Section Head C. Clark Swentzel 8/12/96
Section II, Toxicology Branch II, HED (7509C)
and
for Yiannakis Ioannou, Ph.D. James N. Rowe 8/12/96
Acting Branch Chief, Toxicology Branch II, HED (7509C)

Barcode: D223738; Submission#: S446951; ID#: 7E03489;

MRID#: 433374-01, 433374-02, 433374-03, 433374-04, 433374-05 (original submission MRID# [redacted]; 433374-06; and 428887-05

Chemicals: CGA 154281; Benoxacor

Synonyms: 4-dichloroacetyl-3,4-dihydro-3-methyl-2H-1,4-benzo-xazine (CAS# 98730-04-2).

Action Requested: Review a resubmission of data for review and consideration by the HED Cancer Peer Review Committee submitted by Ciba-Geigy on February 29, 1996. The results of the review of the data package are as follows:

I. C. Breckenridge (August 9, 1993). Summary of Supplemental Toxicity Information Supporting the Registration of CGA-154281 Technical. Ciba Crop Protection, Ciba-Geigy P.O. Box 18300, Greensboro, N.C. 27419. Unpublished (MRID# 4333747-01).

Background: This report is a brief overview of the hazard profile for CGA154281 (Benoxacor), including, acute, developmental, subchronic and chronic toxicity and mutagenicity studies that have been submitted and reviewed by the Agency. A detailed summary of toxicity endpoints and references were presented.

Executive Summary: Data contained in this summary report (MRID433374-01) were previously submitted and reviewed by the Agency, hence no review of this summary study report is necessary. Discussions on individual studies have been evaluated in various DERs. These data have also been thoroughly discussed in conjunction with the evaluation of the significance of forestomach tumors induced in rodents by CGA154281 (Benoxacor) that the registrant submitted to the Agency (MRID428887-05; see DER dated 7/25/96 on this subject matter and the various DERs cited in this DER).

II. M. Bachmann (August 3, 1990) 3-Month Rangefinding Toxicity Study in Mice. Ciba-Geigy Ltd, 4332 Stein, Switzerland. Lab. Study# 891290. MRID#: 43337402, 43337403, and 43337404. Unpublished.

Background: This 13-week feeding toxicity study in mice consists of three reports. A final 13-week feeding toxicity study in mice (MRID#433374-02) plus an amendment (MRID#433374-03) and a supplement (MRID#433374-04) to the final report. The amendment and supplement only dealt with histopathological evaluations of the stomach tissues because of the concern for the stomach papilloma and carcinoma that were found in a chronic feeding study using Benoxacor in mice (MRID#428887-02). The two supplementary study reports are entitled, "Amendment to the Final Report: 3-Month Range-Finding Toxicity Study in Mice (Administered in Food) by M. Bachmann, March 14, 1994 (MRID#433374-03) and "Supplement to 3-Month Range Finding Toxicity Study in Mice. Re-evaluation of Stomach" by J.F. Hardisty, dated August 2, 1994 (Ciba-Geigy Ltd. Study#891290) (MRID#433374-04). This DER included evaluations of all three reports.

Executive Summary: Oral administration of benoxacor (96.8% pure) in mice via the diet at 50, 500, 2000 and 6000 ppm (≈ 7.14, 70.7, 290 and 1100 mg/kg/day for males and 9.53, 99.8, 382 and 1470 mg/kg/day for females) for 92-93 days produced the following major treatment-related effects:

Parameters		0 ppm	50 ppm	500 ppm	2000 ppm	6000 ppm
Body Weight	↓					♂
Water Consumption	↑				♂,♀	♂,♀
Hyperchromic & Macrocytic Anemia	↑					♂
White Blood Cell Count	↑					♀
Platelets	↑				♂,♀	♂,♀
Reticulocyte Count	↑					♂
Aspartate aminotransferase	↑					♂
Alkaline phosphatase	↑					♂
Liver weight	↑				♂,♀	♂,♀
Kidney weight	↑				♂,♀	♂,♀

Spleen weight	↑					♀
Liver necrosis	↑					♂,♀
Interhepatic bileduct hyperplasia	↑					♂,♀
Renal tubular lesion	↑					♂
Renal cortex fibrosis	↑				♂	♂
Renal cortex calcification	↑				♂	♂
Renal tubule atrophy	↑					♂

Based on the above data, the systemic toxicity NOEL is determined to be 500 ppm (70.7 and 99.8 mg/kg/day in males and females, respectively). The systemic toxicity LOEL is 2000 ppm (290 and 382 mg/kg/day in males and females, respectively), based on increased incidence of renal cortex fibrosis and calcification in males, and increased water consumption, increased platelet counts, and increased liver and kidney weights in both males and females.

This study satisfies the EPA's subdivision F guideline requirements (§82-1) for a 90-day Feeding Toxicity Study in mice.

III. Ajit K. Thakur (August 5, 1994). CGA-254281 Technical: Supplement to Subchronic Toxicity Study in Rats. Ciba-Geigy, Greensboro, N.C. Lab. Study #483-291. MRID#433374-05.

Background: This re-evaluation was conducted because of the concern for fore-stomach tumors that were found in chronic feeding studies using CGA154281 (Benoxacor) in mice (MRID#428887-02) and rats (MRID#428887-04).

Dosages: 0, 10, 100, 300, 1000 and 6000 ppm (0, 0.5, 5.0, 15.0, 50.0 and 300 mg/kg/day, based on conversion ratios).

Executive Summary: Based on the re-evaluation and statistical analysis of the incidence of preneoplastic lesions, the increased incidence of nonglandular stomach hyperplasia noted in the 6000 ppm males and females is considered to be related to treatment. The hyperplasia of the limiting ridge region is generally considered as part of the overall changes that occurred within the nonglandular stomach. The statistically significant increased severity (Grade 2) of inflammation of the limiting ridge in the 1000 ppm females is considered a biological variation and is not likely due to treatment.

IV. Peter R. Ryle (August 8, 1994). Supplement to Report: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration in Rats. Lab#509/942145. Ciba-Geigy Ltd, Greensboro, North Carolina. MRID# 433374-06 (original submission MRID#42888-04). Unpublished.

Dosages: 0, 10, 50, 500 and 1000 ppm (0, 0.4, 2.0, 20.6 and 41.0 mg/kg/day in males and 0, 0.6, 2.8, 28.2 and 59.0 mg/kg/day in females).

Background: This supplemental report was submitted to clarify the possible mechanism and the cause of treatment-related microscopic changes seen in the forestomach of the rats.

Executive Summary: Only two 500 ppm females showed microscopical changes in the stomach tissues. One female showed a nonglandular stomach ulcer with associated hyperplasia and hyperkeratosis (#562) and the other exhibited nonglandular stomach minimal hyperkeratosis (limiting ridge) (#622). These two findings did not change the overall conclusion and outcome of an earlier review (DER on A Combined Chronic Toxicity and Carcinogenicity Study in Rats dated 9/15/95: MRID#428887-04).

V. Ian Munroe (August 9, 1993). The Significance of Forestomach Tumors Induced in Rodents by CGA154281. Prepared for Ciba Geigy and conducted by CANTOX Inc. of Canada for Ciba-Geigy, Greensboro, N.C., dated August 9, 1993. Unpublished (MRID# 428887-05).

Background: This report was the result of a one-day symposium on issues of forestomach tumor formations in animals induced by CGA154281 (Benoxacor), organized by Ciba Geigy in May 1993. It was prepared for Ciba Geigy by Dr. Ian Munroe of CANTOX Inc of Canada. This document is a detailed analysis and review of all available data up to 1993 and included a comprehensive toxicological profile of CGA154281 (Benoxacor), based on studies that have been submitted to and reviewed by EPA as well citations from the open literature. The thrust of this report is to show that, based on the current understanding of forestomach tumorigenesis, the lesions induced by CGA154281 (Benoxacor) in animals are not relevant to humans exposed to this compound.

Executive Summary: Based on the discussions and data presented in the study report, the following major conclusions were made by the author:

- The dose response of non-genotoxic carcinogens tends to be non-linear and to show a threshold for tumor induction.
- The progression of lesions induced by non-genotoxic carcinogens shows a precise sequence, induction of hyperplasia, followed by the development of papillomas and finally carcinomas. Latency period for induction of tumors covers a major part of animal's lifetime. Lesions tend to be reversible prior to tumor formation.

- Non-genotoxic forestomach carcinogens induce tumors that are clearly related to antecedent or concomitant induction of cell proliferation and hyperplasia. Genotoxic forestomach carcinogens, do not necessarily induce cell proliferation and are capable of inducing forestomach tumors without inducing a cytotoxic or irritant response in the forestomach epithelium.

- Non-genotoxic forestomach carcinogens only affect this organ, while genotoxic forestomach carcinogens are usually active at many other organ sites indicative of the systematic mode of action of these compounds.

Based on the weight of evidence presented above, the characteristics of the Benoxacor forestomach tumor response are consistent with a nongenotoxic mechanism of action. Benoxacor is a non-genotoxic compound which induces a threshold-dependent, weak tumorigenic effect on the forestomach of rats and mice treated orally with Benoxacor. The forestomach tumors are associated with repeated tissue irritation or cytoxicity and hyperproliferation and do not arise de novo. From the above discussions, on the whole, the tumor responses from butylated hydroxyanisole and benoxacor are similar when considered on a per dose basis.

Human exposure to Benoxacor was estimated to be about 0.000187 mg/kg/day for the U.S. population as a whole and up to 0.000888 mg/kg/day for non-nursing infants (highest of any population subgroup). These exposure estimates assumed a 0.01 ppm residue for all metolachlor-treated commodities, and a 100% market share for these products.

Based on an assumed human exposure of 0.000187 to 0.000888 mg/kg/day and a NOEL of 0.4 mg/kg/day, any human exposures to Benoxacor will be far below (450- to 2,139-fold) the NOEL for forestomach tumors determined in experimental animal studies.

In conclusion, the forestomach tumors induced by benoxacor noted in rodents may not be relevant to humans based on both the mode of mechanism (as shown through comparison to other non-genotoxic and genotoxic forestomach carcinogens) and based on the potential human exposure under the present use pattern.

The DERs of the above noted summaries are attached.

Benoxacor (syn.= 4-dichloroacetyl-3,4-dihydro-3-methyl-2H-1,4-benzoxazine; CAS# 98730-04-2) is not listed in the USEPA's TRI list.

Attachment